The need for new TB diagnostics in children and the way forward

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Childhood TB and control programmes

- Public health approach: focus on sputum smear-positive as identification and treatment of infectious cases will control childhood TB

- Child TB historically afforded a low priority by NTPs:
  - Diagnostic difficulties
  - Usually not infectious (SSP)
  - Limited resources
  - Lack of recording and reporting

But this disregards the impact of TB on childhood morbidity and mortality

Stop TB or Spot TB?

- Child TB under-reported by programmes
  - Children (0-14 years) represent < 2% of total TB case burden managed by NTP
  - Most cases reported are 5-14 years with low proportion of sputum smear “negative” PTB

    e.g. districts in India (2003), Philippines (2008), Cambodia (2005), Indonesia (2009), Vietnam (2006)

- NTP data from communities where all cases managed within NTP structure report that 12-40% of cases are children
  - e.g. Malawi (1998), PNG (2005-6)
- TB a common confirmed cause of respiratory disease and death in children in TB endemic countries
  - autopsy data and clinical data using culture

Burden of child TB

van Rie A et al, Arch Dis Child 1999

Table 1 Age distribution, sex ratio, and type of TB in children in South Africa and the US

	South Africa 1985–94	*US (Alabama) 1983–93*[11]
Child cases as % of new cases		
0–15 years	46	2–5
0–5 years	36.5	
6–15 years	9.5	
Sex ratio (male/female)	0.98	0.94
Age distribution (%)		
0–1 year	37	41
2–4 years	42	22
5–9 years	17	16
10–14 years	4	21
Type of TB (%)		
Pulmonary	98	82.5
Extrapulmonary	2	17.5

The first column gives the results of this study, the second column shows the results of a study conducted by Kimerling *et al.*[11]

Burden of child TB

Harries AD et al, IJTLD 2002; Law I et al, IJTLD (suppl 2) 2008

	Malawi 1998	PNG 2005-6
Child TB cases	2,739	1,977
Proportion of total case load	12%	33%
Age 0-4 years	59%	62%
5-14 years	41%	38%
PTB smear-positive	5%	1%
PTB smear-negative or not done	66%	60%
EPTB	29%	39%
Treatment complete	45%	45%
Death	17%	2%
Default	13%	23%
Unknown	21%	30%

Child TB and the global public health agenda

Childhood tuberculosis: out of control? Donald PR. Curr Opin Pulm Med 2002

INT J TUBERC LUNG DIS 6(5):373–374

EDITORIAL

Childhood tuberculosis: ending the neglect

JR Starke

IN 1956, Katherine H K Hsu asked, "Should primary tuberculosis in children continue to be neglected?"[1] She noted that the advent of isoniazid made possible the successful treatment of early tuberculosis in children to prevent serious pulmonary and extra-pulmonary complications, and to prevent reactivation disease in adolescents and adults. Subsequent scientific study been better performed.[4–7] The main deficiencies were: failure of treatment of latent tuberculosis infection in the child due to poor adherence to therapy; failure to treat children known to have been in contact with a case of tuberculosis before the child developed a positive tuberculin skin test (TST) or disease; and delays or inadequacies in the contact investigation of an

Putting child TB on the global public health agenda

Child TB subgroup of WHO Stop TB Partnership formed 2003

Guidelines development and revisions

WHO Stop TB strategy aims to increase case-finding: 2006

- Routine recording and reporting
- Children recognised as a vulnerable group in need of increased case-finding

Attention to TB/HIV and MDR TB a potential opportunity

International child TB meeting: 2011

- Aiming to address the policy-practice gap

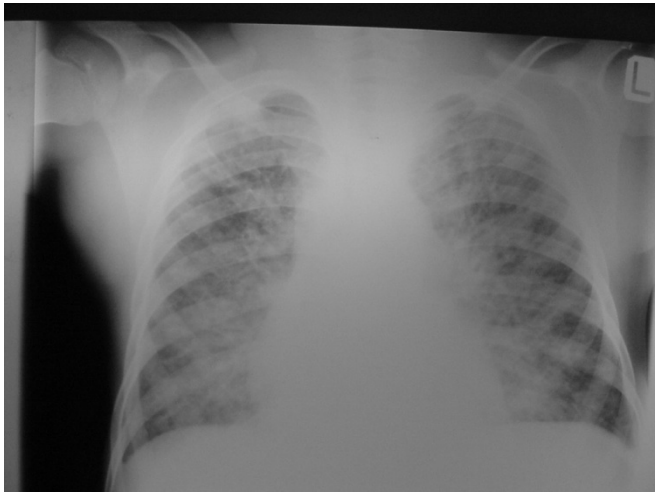
Demystifying childhood TB

Obstacles for children to be diagnosed:

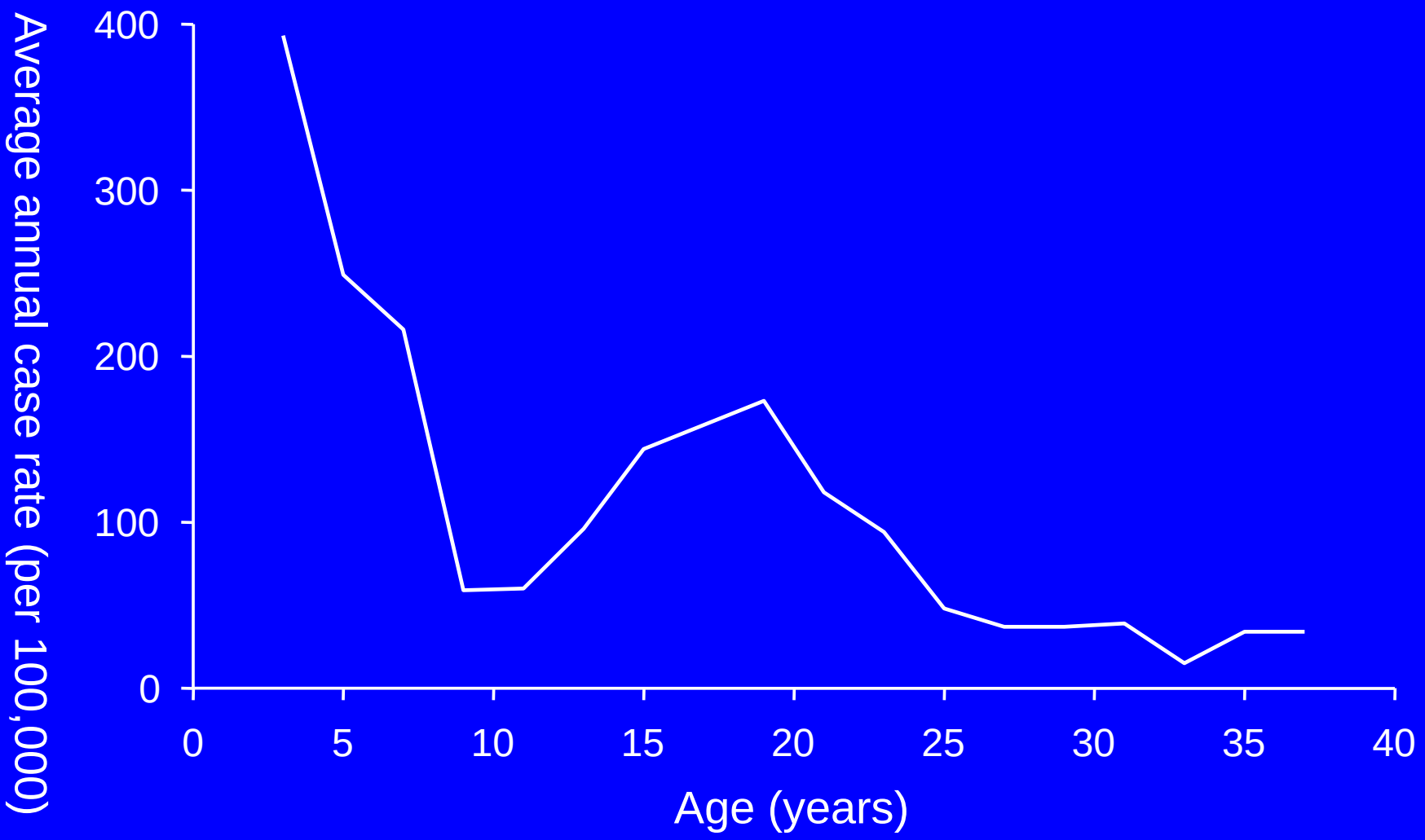
- Lack of diagnostic tools
  - Tuberculin skin test
  - Chest radiography
  - Difficulty in specimens collection and culture
- “**Difficult diagnosis**”

Clinical challenges are the diagnostic challenges

- Young age
- Acute severe pneumonia
- HIV-infected
- Malnourished
- MDR TB



Incidence by age when TB was first diagnosed



Comstock GW, et al. Am J Epidemiol 1974;99:131-8

Improve definition of symptoms

TABLE 4 The value of Combined Variables, Documented at Presentation in Relevant Risk Groups, to Diagnose Pulmonary Tuberculosis in Children

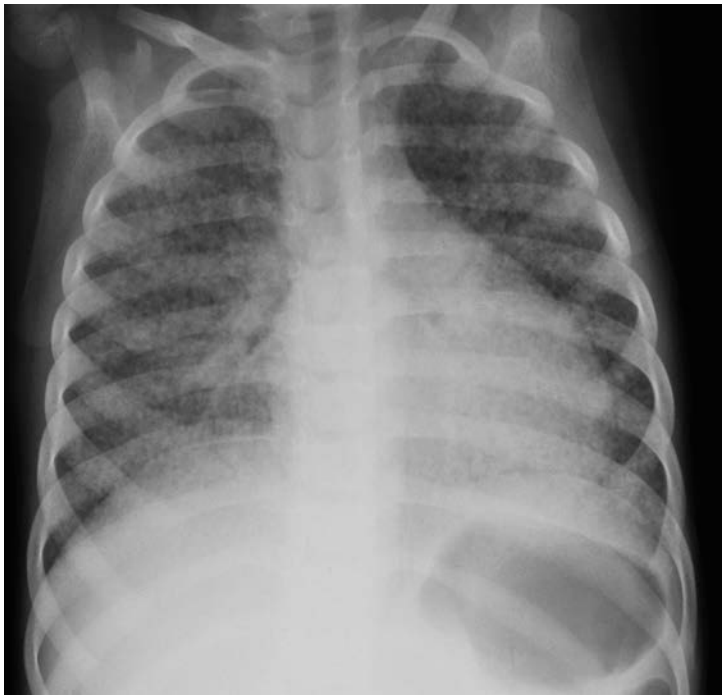
Combined Variables at Presentation[a]	Value		
	Sensitivity	Specificity	PPV
Low-risk children			
≥3 years and HIV uninfected	82.3	90.2	82.3
High-risk children			
<3 years and HIV uninfected	51.8	92.5	90.1
HIV infected (irrespective of age)	56.2	61.8	61.9

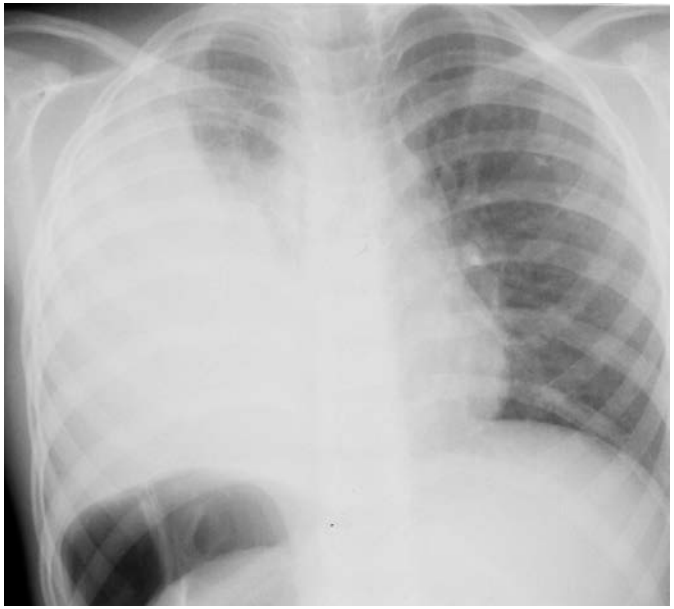
Marais BJ et al. Pediatrics 2006

Types of childhood EPTB disease

	Malawi NTP, 1998	PNG, 2005-6
EPTB cases	808	1097
Lymphadenitis	331 (41%)	342 (31%)
Pleural effusion	101 (12%)	94 (9%)
Spinal	83 (10%)	41 (4%)
Pericarditis	60 (7%)	12 (1%)
Abdominal	39 (5%)	173 (16%)
Miliary	34 (4%)	64 (6%)
Meningitis	30 (4%)	257 (23%)
Bone disease	12 (1%)	15 (1%)
Not indicated/others	118 (14.6%)	99 (9%)

EPTB represented 30% and 39% of childhood TB cases in Malawi and PNG respectively.



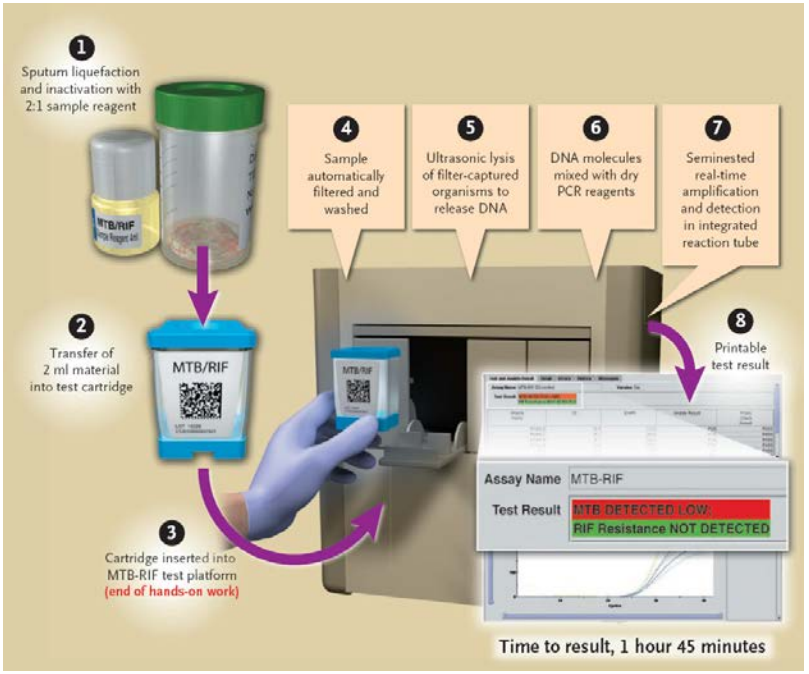



TUBERCULOSIS

	The needs for new diagnostics for children
Clinical	Accurate diagnosis Early diagnosis Pulmonary disease in young children Decentralised care – improved access Improved case definitions Improved outcomes
Research	Improving on current gold standards Distinguishing between infection and disease Vaccine studies Therapeutic trials with clinical outcomes – drugs old and new
NTP	Accurate burden of disease Prospective strategic planning/budget Monitoring and evaluation Decentralised care – improved access Improved outcomes Indicator of TB control

Bugs or biomarkers

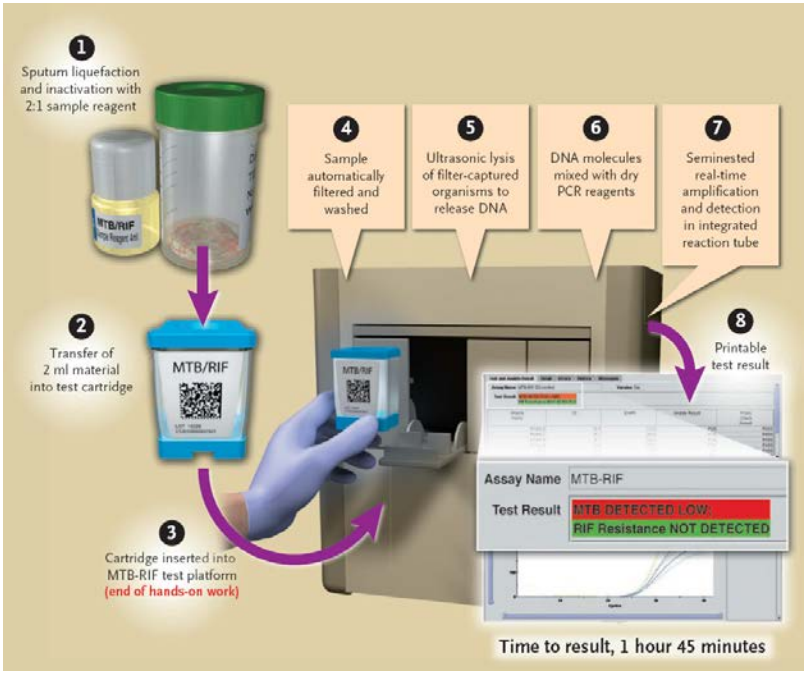
Xpert opinion



from Boehme CC et al, NEJM 2010

Bugs or biomarkers

Xpert opinion



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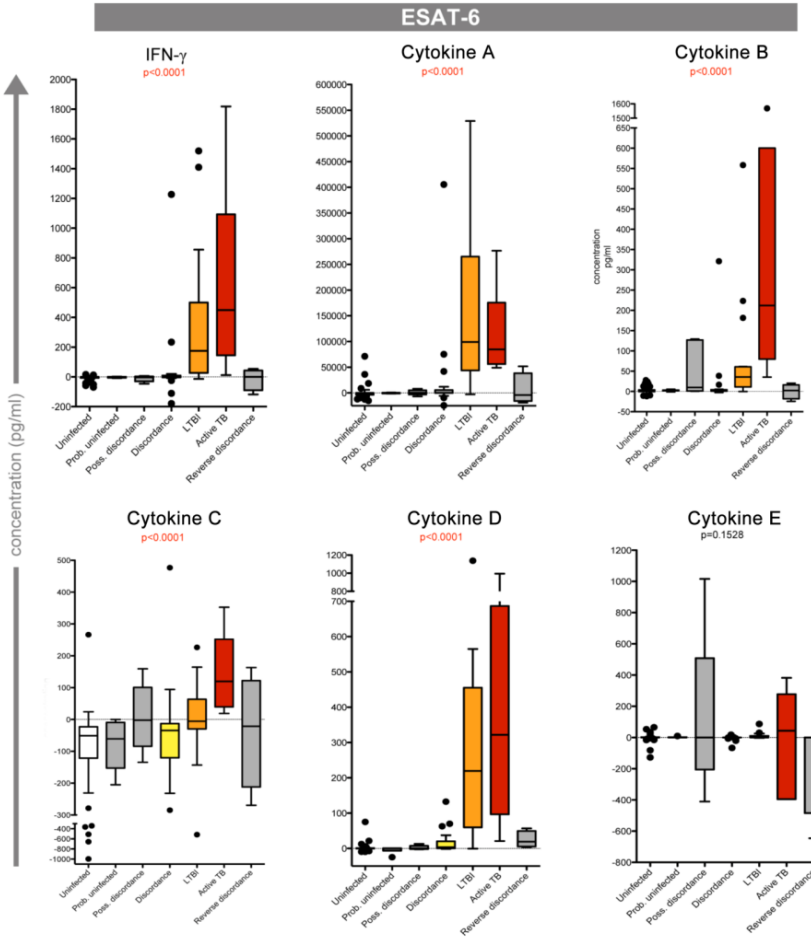

from Terbruegge M, PhD student

Uni of Melbourne 2011

The need for case definitions for research reporting

- Comparison between studies in different settings
- Standardised prospective approach to methodology with optimal yield
- Needed for old and new diagnostics
- Research can improve clinical case definitions
- Ultimate aim is improved care and outcomes

Case definitions for research reporting: MSF, WHO TDR and NIH/NIAID

- Agreement on clinical case definitions for clinical diagnostic studies
- Focus – child < 10 years; intrathoracic disease; symptomatic; co-morbidities
- Phase III studies
- Agreement on culture with Mtb speciation as “gold standard”
- Clinical definitions:
  - confirmed, probable, possible, TB unlikely, not TB

Case definitions for research reporting: MSF, WHO TDR and NIH/NIAID

- Clinical definitions: confirmed, probable, possible, TB unlikely, not TB
  - Clinical features
  - CXR with standardised approach
  - Evidence of exposure/infection
  - Response to treatment

- Different issues for active case-finding studies e.g. vaccine studies, or clinical outcome e.g. drug trials

Case definitions for research reporting

- Current poor performance – “gold” standard

  Nicol M, Zar H. Paediatr Resp Rev 2011

- Clinical definitions not for decisions about TB treatment

- Appendix of definitions for each symptom

- SOPs for methodology e.g. GA, IS

Implementation

- Training tools
- M&E tools for NTPs
- Community-based contact screening
- Integrated
- Opportunities
  - WHO Expanded Stop TB strategy
  - TB/HIV
  - MDR TB
  - New diagnostics

Desk-guide for diagnosis and management of TB in children

International Union Against Tuberculosis and Lung Disease
Health solutions for the poor

Guidance for national tuberculosis programmes on the management of tuberculosis in children